Remarks

Amendments to the Claims

Independent claims 1, 52, and 59 as amended recite a method of screening for the possible presence of a precancerous ovarian lesion or an ovarian cancer in a mammal . . . wherein a detectable increase in amplification of the gene in the sample of the ovarian tissue relative to the control indicates the possible presence of a precancerous ovarian lesion or an ovarian cancer in the mammal. The specification supports these amendments on page 1, lines 13-15 ("The invention pertains to the amplified gene, its encoded proteins, and antibodies, inhibitors, activators and the like in cancer screening and anti-cancer therapy, including ovarian cancer . . . .") and on page 12, lines 21-24 ("'Detecting a cancer' also can refer to obtaining indirect evidence regarding the likelihood of the presence of precancerous or cancerous cells in the animal or assessing the predisposition of a patient to the development of a cancer.").

Claims 1 and 59 are amended to recite a control hepsin gene copy number in a control tissue sample which is not suspected of being precancerous or cancerous. This amendment is supported, *e.g.*, by Example 1.

The amendments do not add new matter.

Rejection Under 35 U.S.C. § 112 ¶ 2

Claims 1, 3, 39, 44, 52, 53, 58-61, 65, 67, 68, and 77-80 stand rejected under 35 U.S.C. § 112 ¶ 2 as indefinite. Applicants respectfully traverse the rejection.

The Office Action contends claims 60 and 63 are unclear because RT-PCR is not used to determine a copy number of DNA. Claims 60 and 63 do not recite using RT-PCR to determine a

copy number of DNA. Claims 60 and 63 recite using RT-PCR to determine indirect measures of hepsin gene copy numbers. As the Office Action acknowledges, RT-PCR can be used to determine levels of mRNA expression. Levels of mRNA expression can provide an indirect measure of gene copy numbers.

The Office Action contends that claims 1, 3, 39, 44, 52, 54, 58-61, 65, 67, 68, and 77-80 are indefinite because the preamble of independent claims 1, 52, and 59 recites "a method for diagnosing," while the last method step recites "indicates the presence of a precancerous lesion or a cancer." Paragraph bridging pages 3 and 4 of the Office Action. Independent claims 1, 52, and 59 as amended recite a method of screening for the possible presence of a precancerous ovarian lesion or an ovarian cancer in a mammal . . . wherein a detectable increase in amplification of the gene in the sample of the ovarian tissue relative to the control indicates the possible presence of a precancerous ovarian lesion or an ovarian cancer in the mammal. The last method step of the amended claims corresponds with the preamble.

Please withdraw the rejection.

Rejection Under 35 U.S.C. § 112 ¶ 1 (written description)

Claims 1, 3, 9, 11, 22, 24, 39, 40, 42, 44, 45, 47, 52, 53, and 58-66 stand rejected under 35 U.S.C. § 112 ¶ 1 as insufficiently described. Applicants respectfully traverse the rejection.

The Office Action contends that the term "hepsin gene" encompasses the hepsin subfamily of genes, which the specification does not describe. Office Action at page 6, lines 1-2. Although claims are given their broadest reasonable interpretation during examination, that interpretation must be consistent with the interpretation that those skilled in the art would reach.

In re Cortright, 165 F.3d 1353, 1359, 49 U.S.P.Q.2d 1464, 1468 (Fed. Cir. 1999). Those skilled in the art would not understand the term "hepsin gene" to encompass other members of the hepsin subfamily of genes. The hepsin subfamily of genes is now known to include hepsin, TMPRSS2, TMPRSS3, TMPRSS4, spinesin, enteropeptidase, and MSPL.[1] Using the human proteins as examples, none of TMPRSS2, TMPRSS3, TMPRSS4, spinesin, enteropeptidase, and MSPL is more than 42% identical to hepsin. See the BLAST alignments in Appendix 1. It is not reasonable to conclude that the recitation "hepsin gene" encompasses genes encoding these other proteins.

Please withdraw the rejection.

Rejection Under 35 U.S.C. § 112 ¶ 1 (enablement)

Claims 1, 3, 9, 11, 22, 24, 40, 42, 44, 45, 47, 52, 53, 58-70, 74, and 77-82 stand rejected under 35 U.S.C. § 112 ¶ 1 as not enabled.[2] Applicants respectfully traverse the rejection.

The Examiner has the initial burden to establish a reasonable basis to question the specification's enabling teachings. *In re Wright*, 999 F.2d 1557, 1562, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993). The Office Action sets forth various reasons why the claims allegedly are not enabled; however, none of these reasons provides a reasonable basis to doubt that the specification is enabling.

[1] Szabo *et al.*, "Type II transmembrane serine proteases," *Thromb. Haemost. 90*, 185-93, 2003, provided with the accompanying Information Disclosure Statement.

[2] As an initial matter, Applicants note that the Office Action contends that "it cannot be reasonably predicted that a method for diagnosing breast cancer in a mammal will predictably function as disclosed." Office Action at page 15, lines 1-3. None of the pending claims is directed to a method of diagnosing breast cancer.

First, the Office Action points to data summarized in Table 4 of the specification, which reports data relating to amplification of the hepsin gene in ovarian, lung, breast, and prostate tumor samples and contends "it is unclear what copy number in a tumor sample is required to be considered 'amplified.'"[3] Office Action at page 10, last ¶ to page 11 ¶ 1. The specification contains a straightforward definition of the term "amplification" in the paragraph bridging pages 15 and 16:

> The term "**amplification**" refers to amplification, duplication, multiplication, or multiple expression of nucleic acids or a gene, *in vivo* or *in vitro*, yielding about 2.5 fold or more copies. For example, amplification of the hepsin gene resulting in a copy number greater than or equal to 2.5 is deemed to have been amplified. However, an increase in hepsin gene copy number less than 2.5 fold can still be considered as an amplification of the gene.

Second, the Office Action faults the specification because it does not provide a working example of gene amplification in a precancerous lesion. Office Action at page 11 ¶ 2. Working examples are not required; moreover, given the specification's teaching that hepsin gene amplification is associated with ovarian cancer, the Office Action provides no reason to doubt that hepsin gene amplification could not be used to screen for precancerous ovarian lesions.

Third, the Office Action faults the specification for not providing an example of analyzing hepsin gene copy number in a non-tumor tissue sample. Office Action at page 11 ¶ 3. In particular, the Office Action faults the specification for not teaching whether non-tumor samples from age- and sex-matched subjects contain hepsin gene amplification. The Office Action's concern about this point is based on pure speculation, unsupported by any evidence that age- or sex-related hepsin gene amplification occurs.

[3] None of the claims which rely on measures of gene amplification are directed to lung, breast, or prostate cancers. Thus, only the hepsin gene amplification data is relevant for independent claims 1, 9, 52, and 62.

Fourth, the Office Action contends that statistically significant hepsin gene amplification is required to enable the claimed methods and that otherwise the false negative rate is too high to reliably diagnose ovarian cancer. Office Action at pages 12-13 and page 15 ¶ 2.[4] Independent claims 1, 52, and 59 as amended are directed to methods of screening for the possible presence of a precancerous ovarian lesion or an ovarian cancer. Screening methods do not require statistical significance or absolute reliability.

Finally, the Office Action contends that the prior art teaches "unpredictability regarding the role of hepsin in biological processes and gene association studies in general." Paragraph bridging pages 13 and 14 of the Office Action. None of the cited prior art is relevant to the claimed methods.

The Examiner cites Lucentini[5] for the proposition that gene association studies typically are wrong. Office Action at page 14, lines 1-8. Lucentini, however, contains no specific teaching about hepsin. Moreover, the frequency with which the hepsin gene is amplified ovarian tumors demonstrates that detecting hepsin gene amplification can indicate the likelihood of the presence of cancer or a pre-cancerous lesion even if the hepsin gene is not found to be causally involved in ovarian cancer.

The Examiner cites Wu[6] as teaching that the physiological role of hepsin remains unknown. Office Action at page 14, lines 8-18. In particular, the Office Action cites Wu as teaching that additional studies are needed to better understand hepsin expression in renal cell

[4] Again, the Office Action refers to data for breast lung and breast cancer, which is not relevant to the claims which rely on measurements hepsin gene copy number.

[5] Lucentini, "Gene association studies typically wrong,' *The Scientist 18*, 1-4, 2004.

[6] Wu *et al.*, "Hepsin and prostate cancer," *Frontiers in Bioscience 12*, 5052-59, 2007.

carcinomas and that the biological significance of hepsin up-regulation in prostate cancer is unclear. None of the claims encompasses a method involving renal carcinomas. In addition, the precise role of hepsin in ovarian, prostate, and lung cancer is not required for the skilled artisan to use amplification of the gene in screening methods for ovarian cancers or precancerous lesions or methods of monitoring treatment efficacy for ovarian cancer or to use hepsin gene overexpression in screening methods for ovarian, prostate, or lung cancers or precancerous lesions.

The Examiner has not met her burden to establish a reasonable basis to question the specification's enabling teachings. *In re Wright*, 999 F.2d at 1562, 27 U.S.P.Q.2d at 1513. See also M.P.E.P. § 2164.04. The evidence of record weighs in favor of enablement.

Please withdraw the rejection.

Respectfully submitted,

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